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<p>(21) International Application Number: PCT/US90/04043 (22) International Filing Date: 18 July 1990 (18.07.90) (30) Priority data: 391,869 10 August 1989 (10.08.89) US (71) Applicant: W.L. GORE & ASSOCIATES, INC. [US/US]; 551 Paper Mill Road, P.O. Box 9206, Newark, DE 19714 (US). (72) Inventors: HULL, John, Richard ; 4053 Fallen Oak Way, Flagstaff, AZ 86004 (US). SHARBER, Norman, Joseph ; 515 North Leroux Street, Flagstaff, AZ 86001 (US).</p>		<p>(74) Agents: WEKER, Dena, M. et al.; W.L. Gore & Associates, Inc., 551 Paper Mill Road, P.O. Box 9206, Newark, DE 19714 (US). (81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent)*, DK (European patent), ES (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent). Published <i>With international search report.</i></p>
<p>(54) Title: A MEDICAL DISPENSING SYSTEM FOR TISSUE ADHESIVE COMPONENTS</p> <div data-bbox="737 1211 1055 1682"> </div> <p>(57) Abstract</p> <p>A medical dispensing system for making tissue adhesive components quickly available for surgical use is described. The process for preparing the medical dispensing system is also described. The medical dispensing system comprises a closed container (10) having a thin frozen coating of a tissue adhesive component (11) dispersed over at least one interior surface. The thin frozen coating of tissue adhesive component (11) may be quickly thawed to be available for surgical use. The container can optionally incorporate a dispensing means such as a syringe (20) or aerosol dispenser (32).</p>		

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A MEDICAL DISPENSING SYSTEM FOR TISSUE ADHESIVE COMPONENTS

FIELD OF THE INVENTION

This invention provides a medical dispensing system for making tissue adhesive components quickly available for surgical use and a process for preparing same.

5

BACKGROUND OF THE INVENTION

Uncontrollable bleeding from traumatic or surgically induced wounds can greatly increase the time needed to surgically treat wounds and can in some cases be life threatening. A variety of hemostatic agents have been developed to decrease wound bleeding. There are two
10 main types: 1) clotting stimulants that stimulate the natural blood clotting mechanisms or provide an excess of a natural clotting component (eg. thrombin), relying on the patient's own blood to provide the other components (eg. fibrinogen), and 2) self-polymerizing tissue adhesives that do not rely on the patient's blood or
15 blood components to assist in hemostasis. The first type includes oxidized cellulose, collagen sponges, gels and powders, cryoprecipitate from cell-free blood plasma, or its major active coagulation ingredients fibrinogen or thrombin. The second type of hemostatic agents include single and multi-component tissue adhesives
20 that differ from clotting stimulants in that they are in themselves self-polymerizing and do not rely on the patient's blood or blood components to play an active role in hemostasis. Such adhesives can be used to adhere tissue to tissue. Tissue adhesives are considered to be more efficacious hemostatic agents than the blood coagulation
25 stimulants.

The earliest tissue adhesives were based on cyanoacrylates, however, tissue toxicity problems with these adhesives has prevented their widespread use.

"Fibrin glue" is currently the most widely used tissue adhesive
30 for hemostasis. Fibrin glue has two major components: fibrinogen and thrombin. Other components such as calcium, calcium salts, Factor XIII and the like may be added if necessary. The components must be kept separate until use because as soon as they are combined, thrombin will rapidly catalyze the conversion of fibrinogen to fibrin monomers
35 which then quickly polymerize into a fibrin network. To control

bleeding, the separate components of fibrin glue are simultaneously applied to the desired site with two separate syringes or with two separate syringes in a common syringe holder. They can also be applied in the form of a spray to stop bleeding from a diffuse source, such as a highly vascularized tissue bed.

There are two common methods of preparing fibrin glue: 1) A cryoprecipitate is obtained from the patient's own cell-free blood plasma and mixed during application with a commercially available bovine thrombin. A disadvantage of this method is that the amount of fibrinogen and other necessary ingredients in the cryoprecipitate varies widely from donor to donor, hence the fibrin glue will be of unknown quality. Another disadvantage is that the blood must be withdrawn from the patient in advance, which may increase the likelihood of the patient requiring a blood transfusion. 2) A commercially available fibrin glue "kit" (Tisseal®, Immuno, A.G., Vienna, Austria) overcomes the quality variability problem. This kit provides a lyophilized form of fibrinogen and thrombin, along with the necessary fluids for reconstitution. One of the components of the kit, fibrinogen, is relatively insoluble. A magnetic stirrer is usually provided to help dissolve the fibrinogen, but the dissolution process can require up to 20 minutes. Very substantial blood loss can occur during that time. This time constraint essentially requires that a surgeon decide beforehand that fibrin glue will be necessary.

It would be desirable to provide means for preparing tissue adhesives such as fibrin glue easily and quickly, so that the preparation will be available for use by the surgeon in a relatively short period of time, for example, within approximately 5 minutes. With such short preparation times, a surgeon does not have to determine in advance that a tissue adhesive will be required.

Tissue adhesives and tissue adhesive components are hereinafter collectively referred to as tissue adhesive components.

SUMMARY OF THE INVENTION

This invention provides a novel medical dispensing system for making tissue adhesive components quickly available for surgical use comprising:

(a) one or more closed containers, each of the containers having at least one interior surface;

(b) a thin frozen coating of a tissue adhesive component on at least one interior surface of said closed containers.

5 The thin frozen coating of tissue adhesive component can be quickly thawed, mixed with another tissue adhesive component if necessary, and immediately applied to a bleeding wound.

The containers may include means for dispensing the tissue adhesive components, in the form of syringes, aerosol dispensers and
10 the like.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows in longitudinal section a cylindrical container having inside a frozen tissue adhesive component in the form of a thin coating dispersed and frozen over the curved interior surface of
15 the container.

Figure 2 shows a double syringe suitable for mixing and applying two separate tissue adhesive components when in liquid states; each syringe is shown in longitudinal section, containing a frozen tissue adhesive component in the form of a thin coating dispersed
20 and frozen over the curved interior surface of the container.

Figure 3 shows in longitudinal section an aerosol dispensing container having inside a frozen tissue adhesive component in the form of a thin coating dispersed and frozen over the curved interior surface of the container.

25

DETAILED DESCRIPTION OF THE INVENTION

It is the purpose of this invention to substantially reduce the amount of time presently required to make tissue adhesives available for surgical use. This is accomplished by placing a solution containing the desired tissue adhesive component or components in a
30 container, closing the container and freezing the solution in the container. The solution can be a liquid or a colloid. The container is rapidly rotated around its axis while being frozen, thus coating at least one interior surface of the container with a thin coating of frozen tissue adhesive component. The tissue adhesive components are

maintained frozen in the form of a thin coating over an interior surface of the container until needed. Thus, the container also serves as a storage device for the frozen tissue adhesive component. In use, the frozen contents of the container or containers are readily
5 thawed, thus making the contents quickly available for application to a bleeding wound.

The advantages of this invention include the quick availability for use compared to the methods currently available. The methods currently available require preparation times on the order of twenty
10 minutes. The present invention provides ready use of the solutions in times significantly less than twenty minutes, often requiring at most five minutes of time.

Figure 1 shows a longitudinal section of a medical dispensing system comprising a container (10) having inside a frozen tissue
15 adhesive component (11) in the form of a thin coating dispersed and frozen over at least one interior surface of the container. This dispensing system was made by placing a solution containing a tissue adhesive component into the container, closing the container and then rotating the container around its axis at a speed high enough to cause
20 the liquid tissue adhesive component to be dispersed in the form of a thin coating over the curved interior surface of the container. The contents of the container were then frozen while the container continued to be rotated.

The container (10) should most preferably be of cylindrical shape.
25 Other shapes may be used if a thin enough coating is produced during spinning to subsequently allow thawing to be accomplished within the desired time. Container shapes other than cylindrical will result in a frozen coating of tissue adhesive component of non-uniform thickness which will subsequently increase the time required for thawing.

30 The time required for thawing the contents of the container is a function of the thickness of the thin coating of frozen tissue adhesive components, the thickness, shape and heat transfer characteristics of the material comprising the container and the method used for thawing the tissue adhesive component. A thin coating
35 is therefore defined as a coating of thickness such that the coating may be thawed, that is made quickly available for surgical use, when heat is applied to the container by a suitable method.

The containers may be of any material such that the contents may be packaged sterile, that adequate physical protection is provided to the contents and that is able to withstand the temperature range necessary for freezing and thawing the contents of the containers.

- 5 Some plastics, metals, and glass are among the materials suitable for this application. The material and the container wall thickness chosen should minimize the time necessary for thawing the thin frozen coating.

- 10 Any suitable method may be utilized to thaw the contents in order to make them quickly available for application, so long as the method chosen does not denature the protein components of the contents or otherwise adversely affect their adhesive characteristics. Both syringe and aerosol type containers that had been partially filled with tissue adhesive components and frozen in the manner previously
15 described have been successfully thawed within five minutes by immersion in 37°C water, exposure to radiant heat from an infrared lamp and simply by holding the container in a human hand. In the case of the heat lamp, the container was rotated along its longitudinal axis in front of the lamp while the surface temperature of the
20 container was monitored with a thermocouple to ensure that the container temperature did not exceed 40°C. An alternate method of thawing would be to use a specially designed heating device that would conduct heat directly to the container while avoiding the possibility of overheating.

- 25 The contents of the container shown in Figure 1 may be dispensed after thawing by, for example, inserting the needle of a syringe through the rubber container cap (12) and withdrawing the contents. The syringe can then be used to apply the contents to the desired surgical site.

- 30 The containers can include means for dispensing the thawed tissue adhesive components. For example, the container may be a syringe. If it is necessary to mix two tissue adhesive components immediately prior to application to tissue, a double barreled mixing syringe (Fig. 2) with a single outlet (23) can be utilized in which each barrel of
35 the syringe contains a different tissue adhesive component (21 and 22). After thawing, the separate components are mixed during application by applying pressure to the common handle (24) typically utilized with the pair of syringe plungers. The separate components

(21 and 22) are thus simultaneously forced into the outlet tube (23) of the syringe assembly. Mixing may be made to occur either within the outlet tube (23) of the syringe assembly or at the tip of the outlet tube, according to the design of the outlet tube. Syringes for this type of application have been available for some time, however, they have not heretofore been utilized for the quick delivery of previously frozen tissue adhesive components.

If a double barreled mixing syringe is utilized for this application it is desirable to load, spin and freeze each syringe (20) individually before installing the syringes into the double barreled distribution device. This is due to the need to spin each syringe along its longitudinal axis during freezing in order to provide an even distribution of the fluid contents over the curved inner surface of each syringe.

The means for dispensing the previously frozen and thawed tissue adhesive components can also be an aerosol or atomized spray. Figure 3 shows a container (30) with an aerosol dispensing mechanism (32), the contents of the container being a thin frozen coating of tissue adhesive component (31). The containers may be pressurized with any suitable propellant so as to enable them to exhaust their contents as an aerosol, or they may be provided with a pump mechanism, preferably hand actuated, in order to deliver the contents in the form of an atomized spray. Either method is suitable when it is desired to uniformly distribute the container's contents over the surface of a surgical site. Where it is desired to mix two components during application, an application mechanism may be utilized that would simultaneously spray the separate contents of two or more containers over the desired surface.

Fibrinogen and thrombin, the basic tissue adhesive components comprising fibrin glue, are the most likely materials for use by the method of this invention. Additives such as calcium, calcium salts, Factor XIII and the like, or anti-fibrinolytic agents such as aprotinin and the like, may be included if necessary before freezing.

EXAMPLE 1

A cylindrical 3 cc polypropylene syringe of about 0.35 inch inside diameter, 0.42 inch outside diameter and 1.9 inch inside length,

containing about 1 cc of cell-free Human Plasma Cryoprecipitate AHF obtained from United Blood Services, Scottsdale, Arizona, was rotated at about 1770 rpm while lowering the container temperature until the contents were frozen. Freezing temperatures were attained by spraying the syringe with carbon dioxide gas. A similar syringe containing about 1 cc of bovine thrombin, obtained from ICN Immuno Biologicals, Lisle, Illinois, was prepared in a similar fashion. The curved interior surfaces of the syringes were found to be coated with a uniform thin frozen layer about 0.032 inches thick of content material. Both syringes were stored frozen at about -20°C until use approximately 15 hours later. The container and contents were then thawed in less than five minutes by holding the container in a human hand. The thawed contents were immediately utilized to retard bleeding at the anastomosis of a prosthetic vascular graft that had been implanted in a greyhound dog as a carotid interposition. Upon completion of the anastomosis, the contents were applied to the anastomosis and suture holes in a fashion similar to the normal application of fibrin glue. Hemostasis was achieved in the same time frame as would be expected using conventionally prepared fibrin glue.

20

EXAMPLE 2

5cc of cell-free human plasma cryoprecipitate was placed into a first cylindrical glass aerosol container of about 1.20 inch inside diameter, 1.43 inch outside diameter and 1.75 inch inside length. 5cc of bovine thrombin was placed into a second cylindrical glass aerosol container of dimensions identical to the first container. Both the cell-free human plasma cryoprecipitate and the bovine thrombin were obtained from the sources described in Example 1. Each container was rotated at about 1600 rpm while subjected to freezing temperatures in the same manner as described in Example 1. The frozen contents coated the curved interior surface of the container to a uniform thickness of about 0.048 inches in each case. The containers are then charged with nitrogen gas as a propellant. After thawing by holding the container in a human hand for less than five minutes, the contents were sprayed simultaneously to retard bleeding in a surgical wound created in a spleen of a greyhound dog. Bleeding from wounds in the spleen and other similar highly vascularized tissue beds is especially

difficult to control. It was found when applying the aerosol that the pressure of the propellant displaced the blood from the surface of the wound, hence allowing the fibrin glue to coagulate directly on the bleeding tissue. This was much more effective in stopping bleeding
5 from such a wound than glue applied from a syringe, which typically results in fibrin glue forming on the surface of the exposed blood rather than on the surface of the wounded tissue. Syringe application may not prevent continued bleeding of this type of wound because fibrin glue applied by syringe will often wash away during bleeding.

We Claim:

1. A medical dispensing system for making tissue adhesive components quickly available for surgical use comprising:
 - (a) one or more closed containers, each of the closed containers having at least one interior surface;
 - (b) a thin frozen coating of a tissue adhesive component on at least one interior surface of each of the closed containers; wherein the tissue adhesive component remains in the form of a thin frozen coating during storage but is thawed immediately before dispensing for surgical use.
2. A medical dispensing system according to claim 1 wherein at least one of the tissue adhesive components comprises fibrinogen.
3. A medical dispensing system according to claim 1 wherein at least one of the tissue adhesive components comprises thrombin.
4. A medical dispensing system according to claim 1 wherein at least one of the tissue adhesive components comprises cell-free human blood cryoprecipitate.
5. A medical dispensing system according to claim 1 wherein the containers are of cylindrical form.
6. A medical dispensing system according to claim 1 wherein said medical dispensing system includes means for quickly thawing the frozen tissue adhesive components.
7. A medical dispensing system according to claim 1 wherein said containers include means for dispensing the tissue adhesive components after thawing.
8. A medical dispensing system according to claim 7 wherein said means for dispensing comprises a syringe.
9. A medical dispensing system according to claim 7 wherein said means for dispensing comprises an aerosol dispenser.
10. A process for preparing a medical dispensing system for making tissue adhesive components quickly available for surgical use comprising:
 - (a) placing one or more tissue adhesive components in liquid state into one or more containers, each container having at least one interior surface;
 - (b) closing said containers;
 - (c) rotating said containers and tissue adhesive components at a rate fast enough to cause said tissue adhesive components to

form a thin coating on at least one interior surface of each container; and

(d) freezing said tissue adhesive components during rotation so as to form thin coatings of frozen tissue adhesive

5 components.

11. A process according to claim 10 wherein one of the tissue adhesive components is fibrinogen.
12. A process according to claim 10 wherein one of the tissue adhesive components is thrombin.

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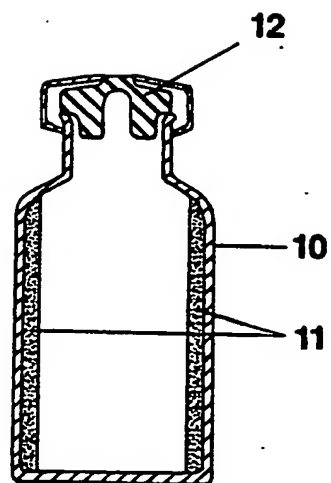


FIG. 1

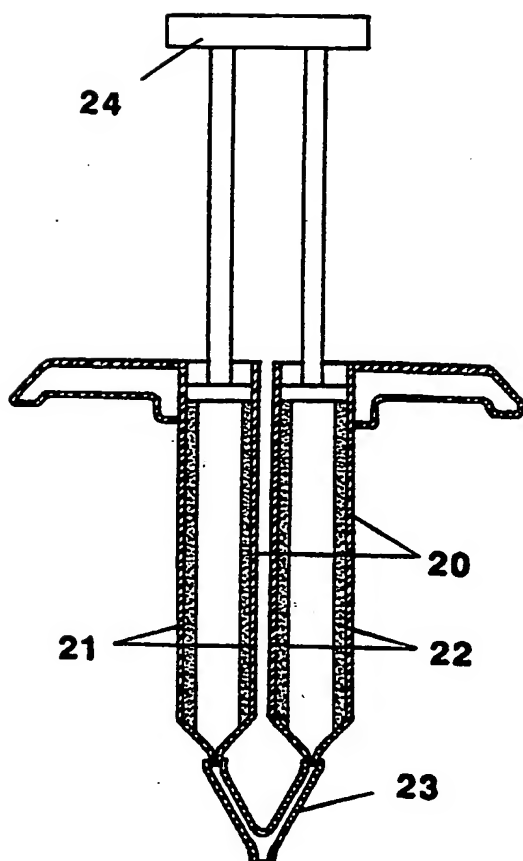


FIG. 2

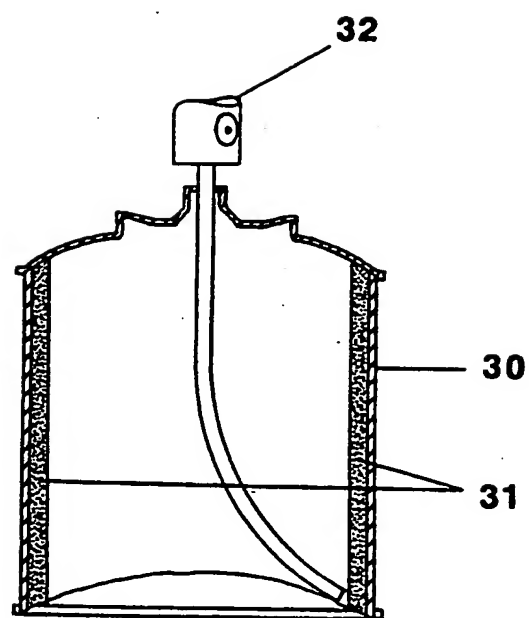


FIG. 3

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 90/04043

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC⁵: A 61 J 1/00, A 61 L 25/00, F 25 C 1/10, A 61 M 5/18,
A 61 M 11/00, B 65 D 81/18

II. FIELDS SEARCHED

Minimum Documentation Searched ⁷

Classification System

Classification Symbols

IPC⁵

A 61 L, A 61 J, B 65 D, A 61 B, F 25 C

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched ⁸

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	Adv. Biomater., volume 3, 1982, H. Redl et al.: "Background and methods of "fibrin sealing", pages 669-676 see page 669, line 1 - page 670, line 4; page 672, lines 17-36; figure 6 --	1-3,5,7-12
Y	US, A, 2655007 (LAZAR) 13 October 1953 see column 1, lines 1-26; column 5, lines 1-11; claims 4,5; figures 1-5 --	1-3,5,7-12
A	US, A, 4139992 (FRASER) 20 February 1979 see abstract; column 1, lines 9-16; figure 1 -- ./.	1,5,10

* Special categories of cited documents: ¹⁰

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

16th October 1990

Date of Mailing of this International Search Report

- 6 NOV 1990

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

MISS D. S. KOWALCZYK

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	GB, A, 2042556 (IMMUNO) 24 September 1980 see page 1, lines 5-25, 76-121; claims 1,8,11,13 --	2-4,11,12
A	FR, A, 1565256 (3M) 25 April 1969 see claims A.1, A.2; figures --	7,9
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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9004043

SA 38838

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 29/10/90. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 2655007		None	
US-A- 4139992	20-02-79	None	
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US-A- 3240328		None	
GB-A- 1103534		None	